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Office of Vermont Health Access

Therapeutic Class Review
Agents for Opioid Detox

Overview/Summary

Opioid dependence is a chronic medical illness marked by high rates of relapse. Detoxification is the first step in treatment of opioid dependence with longer term pharmacological therapies used to sustain abstinence and prevent relapse. Long term addiction treatment can take many forms including abstinence-based treatment, opioid antagonist (naltrexone) treatment, or maintenance with an opioid agonist (methadone) or an opioid agonist/antagonist (buprenorphine). Maintenance pharmacotherapy varies in the mechanism in which abstinence is reinforced. The use of opioid agonists suppress cravings and withdrawal symptoms while utilization of an antagonist prevents the user from experiencing beneficial effects with subsequent opioid use.[1]

Naltrexone is available as an oral tablet (Revia®)[2], as well as an injectable extended release suspension for intramuscular use (Vivitrol®)[3]. The oral formulation is Food and Drug Administration (FDA) approved for the blockade of the effects of exogenously administered opioids as well as the treatment of alcohol dependence[2]. The intramuscular (IM) formulation is FDA approved for the treatment of alcohol dependence in patients who are able to abstain from alcohol[3]. The use of naltrexone for alcohol dependence is noted but not discussed within this review.

This review focuses on the use of naltrexone, a pure opioid antagonist, in the treatment of opioid dependence. It hinders the activity of opioids by competitive binding at opioid receptors. Naltrexone IM (Vivitrol®) is not discussed in this review.

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Naltrexone (Revia®)	Opioid antagonist	✔

Indications

Table 2. Food and Drug Administration Approved Indications[2]

Generic Name	Treatment of Alcohol Dependence	Blockade of the Effects of Exogenously Administered Opioids
Naltrexone	✔	✔

Pharmacokinetics

Table 3. Pharmacokinetics[2,4-5]

Generic Name	Bioavailability (%)	Absorption (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Naltrexone	5-40	96	53-79 (also as metabolites); <2 unchanged	Yes; 6-beta-naltrexol	4 (parent drug); 13 (metabolite)

Clinical Trials

Results of clinical trials for the use of naltrexone for opioid dependence are mixed at best. A Cochrane review of oral naltrexone maintenance treatment for opioid dependence concluded that there was no clear benefit of naltrexone in terms of retention in treatment, side effects, or relapse. This was based on a review of ten studies with 696 total participants.[6] In another systematic review, eleven clinical trials were reviewed and the authors arrived at a similar conclusion; that there is insufficient evidence to justify the use of naltrexone in the maintenance treatment of opioid addicts.[7] A comparison of the specific trials reviewed for each publication shows that seven of the trials were included in both reviews. Details of these trials are outlined in Table 4.

There are a number of limitations to the clinical trials conducted with naltrexone. The number of participants in many of the studies is small as a result of drop-outs and loss to follow-up. Due to its mechanism of action, and the lack of physiological dependence, subjects can discontinue taking naltrexone at any time without experiencing withdrawal symptoms. Additionally, many of the studies do not compare naltrexone to other pharmacological agents or even to placebo. The use of a placebo in these trials does not ensure blinding because subjects can "test" by injecting heroin shortly after randomization to determine whether or not they are receiving active drug. It is for these reasons that many of the authors have concluded that there is limits to the utility of naltrexone in opioid-addicted patients. Highly motivated patients or those that have legal pressures to remain opioid free may have better results with naltrexone treatment.[8]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Cornish et al[8] Naltrexone 25 mg daily for 2 days, then 50 mg daily for 3 days, then 100-150 mg; patients also received counseling vs counseling alone	OL, RCT Individuals assigned to a minimum of 2 years federal probation or parole and were being supervised by probation officers	N=51 6 months	Primary: Efficacy determined by reduced opioid use and incidence of re-arrest Secondary: Not reported	Primary: Naltrexone subjects had an average of 8% opioid-positive specimens while controls averaged 30% positive (P<0.05). Twenty-six percent of naltrexone subjects were reincarcerated for probation violations compared to 56% of controls (P=0.05). Secondary: Not reported
Curren et al[9] Naltrexone six days a week for the first two months, then three times a week (doses not specified) vs placebo	DB, PC, RCT Subjects were parolees or probationers; mean age 26 years	N=38 9 months	Primary: Acceptance rate, retention in treatment, relapse Secondary: Side effects	Primary: Using length of treatment as an indicator of acceptance, naltrexone subjects' participation in the study was 80.9 days and placebo subjects for 92.1 days. This duration appears to favor placebo subjects, however their length of treatment is confounded by subjects using heroin for a period of two to four weeks. Only 4 subjects from the 38 completed the full nine months of study. This was evenly divided between the naltrexone and placebo groups. Secondary: Five subjects were terminated due to side effects and were taking naltrexone.
Ladewig U[10] Naltrexone 50 mg daily for 3 weeks, then 100 mg on Monday, 100 mg on Wednesday, and 150 mg on Friday; patients also received psychotherapy vs psychotherapy alone	OL, RCT Males and females age 20-35 who were opioid free for at least 10 days	N=20 6 weeks	Primary: Retention in treatment Secondary: Not reported	Primary: 19 participants were included in final data. Six out of fourteen (43%) participants in the naltrexone group compared to 3/5 (60%) in the psychosocial alone group, had positive urine samples at the end of the study (RR, 0.71; 95% CI, 0.28 to 1.82; a difference that was not statistically significant. Seven out of fourteen (50%) participants in the naltrexone plus psychosocial group compared to 3/5 (60%) in psychosocial group had at least one side effect (RR, 0.83; 95% CI, 0.34 to 2.02 a difference that was not statistically significant. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Lerner et al[11] Naltrexone 12.5-50 mg daily for 7 days, then 100 mg on Monday, 100 mg on Wednesday, and 150 mg on Friday vs placebo	DB, PC, RCT Subjects were newly abstinent after opioid detoxification, opioid free for 1-2 weeks, and a mean age of 26.6 years	N=31 2 months	Primary: Number of subjects opioid free at the end of treatment and 1 year follow-up retention rates Secondary: Not reported	Primary: Naltrexone did not appear to be more efficacious compared to placebo with regards to retention rate. In the Naltrexone group (n=15), 9 individuals finished the two-month treatment, and 8 remained opioid-free for a year. In the placebo group (n=16), 8 individuals finished the 2 month trial and 6 remained opioid-free for a year. Secondary: Not reported
Rawson et al[12] Naltrexone 50 mg daily for 2 weeks, then 50 mg twice a week and 100 mg on Saturday for 6 weeks, then 100 mg twice a week and 150 mg on Friday vs naltrexone regimen plus behavior therapy vs behavior therapy alone	OL, RCT Subjects were male heroin addicts with a mean age of 25.9 years and the mean years addicted to heroin was 7.9	N=181 10 months	Primary: Retention in treatment, and relapse Secondary: Re-incarceration	Primary: There was no statistically significant difference between the naltrexone group when compared to the naltrexone plus therapy group for the retention in treatment (RR, 0.94; 95% CI, 0.59 to 1.48). Seventeen percent of participants in the naltrexone group compared to 27% of the behavior therapy alone group had relapsed to the use of heroin at the end of the follow up (RR, 0.65; 95% CI, 0.19 to 2.22; a difference that was not statistically significant). Forty percent of participants in the naltrexone plus therapy group compared to 27% of participants in the therapy alone group relapsed to use of heroin at the end of the follow up (RR, 1.50; 95% CI, 0.55 to 4.06; a difference that was not statistically significant. Secondary: Twenty six percent of participants in the naltrexone group compared to 40% in the behavior therapy alone group were re-incarcerated during the study. The difference between groups was not statistically significant but there was a trend in favor of the naltrexone treatment group. This trend was also seen in the comparison of naltrexone plus therapy versus therapy alone.
San et al[13] Naltrexone 350 mg per week (given 100-100-150)	DB, PC, RCT Male and female subjects, age 18 to	N=50 1 year	Primary: Degree of treatment acceptance,	Primary: Therapeutic success was achieved in 4 of the 28 naltrexone-treated patients and in 8 of the 22 placebo-treated patients. This clinically relevant difference was not statistically significant because of the small number of patients included

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	30, who fulfilled DSM-III-R criteria for opioid dependence		percentage of relapse in heroin consumption, presence of side effects, and overall retention on naltrexone Secondary: Not reported	in each category, which gave rise to a beta error of 65%. Patients in the placebo group continued treatment for a longer period (8.9±4.8 vs 7.5±5.7 weeks) and generally attended a larger number of visits (4.4±1.8 vs 3.1±2.0 visits) than patients in the naltrexone group. These differences were neither statistically nor clinically significant. A total of 101 side effects were observed (32 in the naltrexone group and 69 in the placebo group). The most common were fatigue, nausea, vomiting, headache, diarrhea, trembling, muscle fatigue and dry mouth. Overall retention rate at 6 months was 27.9% (12/43 patients, drop-outs excluded). Differences between retention rates in the naltrexone group (17.4%; 4/23 patients) and placebo group (40.0%; 8/20 patients) were not statistically significant. Six months after completion of treatment (1 year after naltrexone inductions), the percentage of drug free patients was 32% in the naltrexone group and 36% in the placebo group. Secondary: Not reported
Shufman et al[14] Naltrexone 25 mg twice a week for 2 weeks, then 50 mg three times a week vs placebo	DB, RCT, PC Male heroin addicts that had successfully completed a detoxification program and remained abstinent for at least ten days	N=32 12 weeks	Primary: Retention and relapse Secondary: Not reported	Primary: Fewer heroin-positive urine tests were found the naltrexone group than in the placebo group. Throughout the entire study, the number of drug-free patients in the naltrexone group was higher than in the placebo group. The naltrexone group showed a significant improvement in most psychological parameters as compared with the placebo group. No differences were found in compliance or ratio of adverse effects between the naltrexone and placebo groups no statistical values provided). Secondary: Not reported

Study abbreviations: CI=confidence interval, DB=double-blind, OL=open-label, PC=placebo-controlled, RCT=randomized controlled trial, RR=relative risk
Miscellaneous abbreviations: DSM-III-R=Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised

Table 5. Special Populations[2]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Naltrexone	Not studied in the elderly. Safety and efficacy in pediatric patients under the age of 18 years old have not been established.	Naltrexone and its primary metabolite are excreted primarily in the urine, and caution is recommended in administering the drug to patients with renal impairment.	Caution should be exercised when naltrexone is administered to patients with liver disease.	C	Yes (% unknown)

Adverse Drug Events

Adverse reactions that have been reported both at baseline and during various naltrexone clinical trials for the treatment of opioid addiction are listed below in Table 6.

Table 6. Adverse Drug Events [2]

Adverse Event	Reported Frequency (%)
Cardiovascular	
Edema	✔
Increased blood pressure	✔
Non-specific electrocardiogram changes	✔
Nose bleeds	✔
Palpitations	✔
Phlebitis	✔
Tachycardia	✔
Dermatologic	
Acne	✔
Alopecia	✔
Athletes foot	✔
Cold sores	✔
Oily skin	✔
Pruritus	✔
Skin rash	<10
Gastrointestinal	
Abdominal pain/cramps	>10
Constipation	<10
Diarrhea	<10
Excessive gas	✔
Hemorrhoids	✔
Loss of appetite	<10
Nausea and/or vomiting	>10
Ulcer	✔
Genitourinary	
Delayed ejaculation	<10
Increased frequency of, or discomfort during urination	✔
Increased or decreased sexual interest	✔
Musculoskeletal	
Joint and muscle pain	>10
Painful shoulders, legs, or knees	✔

Adverse Event	Reported Frequency (%)
Tremors	✔
Twitching	✔
Psychiatric	
Anxiety	>10
Confusion	✔
Depression	✔
Difficulty sleeping	>10
Disorientation	✔
Fatigue	✔
Feeling down	<10
Hallucinations	✔
Irritability	<10
Nervousness	>10
Nightmares/bad dreams	✔
Paranoia	✔
Restlessness	✔
Respiratory	
Cough	✔
Excess mucus or phlegm	✔
Heavy breathing	✔
Hoarseness	✔
Nasal congestion	✔
Rhinorrhea	✔
Shortness of breath	✔
Sinus trouble	✔
Sneezing	✔
Sore throat	✔
Special Senses	
Ears: clogged, aching, tinnitus	✔
Eyes: blurred, burning, light sensitive, swollen, aching, strained	✔
Other	
Chills	<10
Cold feet	✔
Dry mouth	✔
Fever	✔
Headache	>10
Head “pounding”	✔
Hot spells	✔
Increased appetite	✔
Increased energy	<10
Increased thirst	<10
Inguinal pain	✔
Low energy	>10
Side pains	✔
Somnolence	✔
Swollen glands	✔
Weight gain	✔
Weight loss	✔
Yawning	✔

✔ Incidence not specified or <1%.

Contraindications/Precautions[2]

Naltrexone causes immediate withdrawal symptoms if administered prior to detoxification. Therefore, naltrexone is contraindicated in patients receiving opioid analgesics, patients currently dependent on opioids, or patients in acute opioid withdrawal. Additionally, naltrexone is contraindicated in any individual with acute hepatitis or liver failure and has been assigned a black box warning for use in this patient population.

Black Box Warning Naltrexone

WARNING
Naltrexone has the capacity to cause hepatocellular injury when given in excessive doses. Naltrexone is contraindicated in acute hepatitis or liver failure, and its use in patients with active liver disease must be carefully considered in light of its hepatotoxic effects. The margin of separation between the apparently safe dose of naltrexone and the dose causing hepatic injury appears to be only five-fold or less. Naltrexone does not appear to be a hepatotoxin at the recommended doses. Patients should be warned of the risk of hepatic injury and advised to stop the use of naltrexone and seek medical attention if they experience symptoms of acute hepatitis.

Drug Interactions[2]

Studies to evaluate possible interactions between naltrexone and drugs other than opiates have not been performed. Consequently, caution is advised if the concomitant administration of naltrexone and other drugs is required.

The safety and efficacy of concomitant use of naltrexone and disulfiram is unknown, and the concomitant use of two potentially hepatotoxic medications is not ordinarily recommended unless the probable benefits outweigh the known risks.

Lethergy and somnolence have been reported following doses of naltrexone and thioridazine.

Dosage and Administration[2]

Treatment should not be attempted unless the patient has remained opioid-free for at least 7-10 days. Self-reporting of abstinence from opioids in opioid addicts should be verified by analysis of the patient's urine for absence of opioids. The patient should not be manifesting withdrawal signs or reporting withdrawal symptoms. If there is any question of occult opioid dependence, a naloxone challenge test should be performed. If signs of opioid withdrawal are still observed following naloxone challenge, treatment with naltrexone should not be attempted. The naloxone challenge is described below under the "other key facts" heading.

Once a patient has been started and stabilized on naltrexone 50 mg daily, a flexible dosing regimen may need to be employed especially in cases of supervised administration. Thus, patients may receive 50 mg of naltrexone every weekday with a 100 mg dose on Saturday, 100 mg every other day, or 150 mg every third day.[2]

Table 7. Dosing and Administration[2]

Generic Name	Adult Dose	Pediatric Dose	Availability
Naltrexone	Initial, 25 mg daily; maintenance, 50 mg daily (alternate dosing schedules may be employed; see above)	Safety and efficacy in pediatric patients under the age of 18 years old have not been established.	Tablet: 50 mg

Other Key Facts

Naloxone Challenge Test[2]

The naloxone challenge test should not be performed in a patient showing clinical signs or symptoms of opioid withdrawal, or in a patient whose urine contains opioids. The naloxone challenge test may be administered intravenously or subcutaneously as follows:

Intravenous: Inject 0.2 mg naloxone; observe for 30 seconds for signs or symptoms of withdrawal. If no evidence of withdrawal, inject 0.6 mg of naloxone. Observe for an additional 20 minutes.

Subcutaneous: Administer 0.8 mg naloxone. Observe for 20 minutes for signs or symptoms of withdrawal.

If signs or symptoms of withdrawal appear, the test is positive and no additional naloxone should be administered. Naltrexone should not be administered if the naloxone challenge test is positive.

Clinical Guidelines

Table 8. Clinical Guidelines

Clinical Guideline	Recommendations
National Institute for Health and Clinical Excellence: **Naltrexone for the Management of Opioid Dependence (2007)**[15]	• Naltrexone is recommended as a treatment option in detoxified formerly opioid-dependent people who are highly motivated to remain in an abstinence program. • Naltrexone should only be administered under adequate supervision to people who have been fully informed of the potential adverse effects of treatment. It should be given as part of a programme of supportive care. • The effectiveness of naltrexone in preventing opioid misuse in people being treated should be reviewed regularly. Discontinuation of naltrexone treatment should be considered if there is evidence of such misuse.
Australian Government Department of Health and Ageing: **Clinical Guidelines and Procedures for the Use of Naltrexone in the Management of Opioid Dependence (2003)**[16]	• The usual maintenance dose of naltrexone is 50 mg daily. However, 25 mg daily produces adequate blockade of opioid receptors and may be used in patients who experience side-effects from 50 mg/day. • Treatment for dependence is a long-term process. The optimal duration for treatment with naltrexone is unknown but patients should generally be encouraged to take naltrexone for at least 6 months. • It is recommended that patients on naltrexone treatment should receive clinical reviews weekly during the first month of treatment, then monthly as required. • Patients that relapse may benefit from residential treatment or methadone or buprenorphine maintenance treatment.

Conclusions

Naltrexone is an orally administered opioid antagonist that may be used in the treatment of opioid addiction. In patients that have successfully detoxified from opioids, naltrexone can be utilized as maintenance therapy to prevent relapse. Its antagonist mechanism of action blocks receptors from opioids and therefore the patient receives no pleasurable effect when opioids are administered. However, its utility has proven to be limited and in a number of studies, no more effective than placebo or psychosocial behavior. Naltrexone does however provide an alternative pharmacological therapy for maintenance of opioid abstinence and may be useful in those patients that cannot take an opioid agonist or that are highly motivated to remain abstinence free. Naltrexone is available generically in an oral dosage form.

Recommendations

Based on the information presented in the review above and cost considerations, no changes are recommended to the current approval criteria.

Generic oral naltrexone is preferred on The Office of Vermont Health Access (OVHA) preferred drug list.

Revia® requires prior authorization with the following approval criteria:
- The patient has had a documented intolerance to the generic product.

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